Adrenal insufficiency and exogenous Cushing's syndrome in a patient receiving inhaled fluticasone and ritonavir

Insuficiencia adrenal y exógenos en un paciente con síndrome de down que recibe fluticasona inhalada y ritonavir

Iatrogenic Cushing's syndrome has been frequently described in patients receiving treatment with oral steroid drugs. However, this is uncommon with inhaled corticosteroids (ICS).[1]

Hepatic metabolism of inhaled corticosteroids takes place via cytochrome P450 3A4. Consequently, it can be decreased by enzyme inhibitors such as itraconazole or ritonavir, thus leading to an increased bioavailability. This applies especially to fluticasone, which has a longer half-life and is very lipophilic.[1,2]

We present the case of a 48-year-old woman, whose endocrinologic evaluation was requested during hospitalization in January 2014 in the Internal Medicine Department. The patient was morbidly obese (BMI 52 kg/m^2), had hypertension and hypercholesterolemia. She had been diagnosed in 1991 with HIV infection (stage C3), and had had multiple opportunistic infections. At present she was under treatment with darunavir (800 mg/day), ritonavir (100 mg/day) and lamivudine (300 mg/day).

The patient also had severe sleep apnea syndrome and asthma. For the latter, she was under treatment with salbutamol 1 puff of 100 mcg/8 h, zafirlukast 20 mg/12 h and salmeterol/fluticasone 25/250 mcg 2 puffs/12 h, since June 2011.

In January 2014, the patient was admitted to the Intensive Care Unit due to a massive upper gastrointestinal bleeding secondary to erosive gastritis due to anti-inflammatory drugs, which required support with vasoactive drugs during the first 72 h.

However, one week after her admission, the patient started to present hypoglycemia and arterial hypotension, together with intense asthenia and weakness in inferior limbs. The physical examination showed a cushingoid appearance with central obesity, moon face, dorsal hump, red striae and facial hirsutism. Blood tests were carried out, showing normal renal function, hepatic function and electrolytes; albumin levels were between 2.5 g/dl and 2.9 g/dl during hospitalization. Hormone levels showed the following results: morning cortisol: 3.1 μg/dl (before 10 h a.m.: 3.7–19.4 μg/dl), adrenocorticotropic hormone (ACTH) 6.7 pg/ml (<46 pg/ml), follicle stimulating hormone (FSH) 3.11 mUI/ml, Luteinizing Hormone (LH) 0.21 mUI/ml, estradiol 17 pg/ml, testosterone < 0.08 ng/ml (0.10–0.56 ng/ml) and dehydroepiandrosterone < 0.15 mcg/ml, TSH 4.4 uUI/ml (0.35–4.9 uUI/ml), T3L 2.06 pg/ml (1.7–3.7 pg/ml) and T4L 0.97 ng/dl (0.7–1.4 ng/dl). The remaining pituitary axis was normal. Synacthen test was not performed because the patient was at the time hemodynamically unstable and early morning low serum cortisol concentration equal to or less than 3 mcg/dL is strongly suggestive of adrenal insufficiency. It is also important to note that decreased levels of albumin have been associated to a decrease in protein-bound cortisol, with therefore a relatively lower total but appropiate free cortisol. However, this has been described in patients with albumin lower than 2 mg/dl, which was not the case of our patient.[3]

Therefore, according to the mentioned results, the patient was diagnosed with acute adrenal insufficiency and hypogonadotropic hypogonadism.

A cranial CT focused on the sella turcica ruled out structural disease (MRI could not be done due to the morbid obesity of the patient). However, if we recall her usual treatment at home, the patient had been receiving inhaled fluticasone since 2011, which had not been administered since the gastrointestinal bleeding had started.

Additionally, she was under treatment with ritonavir, an inhibitor of cytochrome P450 3A4 and, as mentioned, both treatments combined can increase the half-life of fluticasone, thus leading to a iatrogenic Cushing's syndrome, and an acute adrenal insufficiency after sudden removal of the inhaled steroids.

Hypogonadotropic hypogonadism could be secondary to the HIV infection or the critical illness, but could also be justified in the context of the iatrogenic Cushing's syndrome due to inhaled fluticasone.[4,5]

After the diagnosis of acute adrenal insufficiency, the patient was started on intravenous hydrocortisone 100 mg/8 h, recovering from her asthenia and achieving normal blood pressure and euglycemia. Hydrocortisone was then tapered to lower intravenous doses and finally replaced by oral steroids. Inhaled steroid drugs were removed, and she was discharged under treatment with salmeterol 2 puffs/12 h, ipratropium 1 puff/day and salbutamol if needed. HIV treatment with ritonavir was continued. Two months after starting steroid replacement therapy, the patient's cortisol was 13 μg/dl (before 10 a.m.: 3.7–19.4 μg/dl) and ACTH 36.9 pg/ml (<46 pg/ml). Unfortunately, we do not have gonadotropins levels at the time, or posterior cortisol levels or synacthen test, as the patient stopped attending her appointments at the Endocrinology Department.

Adrenal insufficiency secondary to removal of inhaled steroid drugs is uncommon, especially if the doses are low. However, its frequency can increase if the patient is also under treatment with inhibitors of cytochrome P450 3A-4, such as protease inhibitors or triazoles. The liver metabolism of corticosteroids depends on the mentioned cytochrome, and therefore its inhibition may increase the bioavailability of steroid drugs.[1] Fluticasone has a higher lipophilicity and longer elimination half-life, and therefore has a greater suppressing effect on the adrenal axis.[2]

In a pharmacovigilance retrospective study conducted in France, 11,783 physicians were contacted, in order to establish the prevalence of adrenal insufficiency over a 5-year period in patients treated with inhaled steroid drugs. 46 cases were reported, 52% of them with fluticasone. It should be noted that drug interactions were suspected in 12 cases: 6 for concomitant use of fluticasone and ritonavir, 4 for fluticasone and itraconazole, and 2 for budesonide with itraconazole.[6] However, it has been shown that the doses of ICS reported to interact with PI are within the recommended daily dose range.[6,7] Nevertheless, the duration of

corticosteroids-PI co-administration prior to onset of symptoms is highly variable, ranging from ten days to five years.[7]

In order to prevent developing Cushing's syndrome in patients on ritonavir who require inhaled or intranasal corticosteroids, fluticasone, mometasone and ciclosonide should be avoided. Safer options include beclomethasone, budesonide, triamcinolone and flunisolide prescribed at the lowest possible doses. However, if possible, substituting ICS with oral montelukast or non-steroidal bronchodilators should be considered. Another option would be initiating or changing the PI to another antiretroviral agent that does not inhibit the cytochrome 3A4 (such as non-nucleoside reverse transcriptase inhibitors or integrase inhibitors), if the history of drug resistance and previous treatments of the patient allows this option.[2,6]

However, if inhaled steroid treatment is maintained together with ritonavir or other cytochrome 3A4 inhibitors, the patient should be monitored for signs of Cushing's syndrome, and when ICS are discontinued, gradual tapering may be required in order to avoid adrenal insufficiency. Some authors, such as Hopkins et al. suggest checking serum morning cortisol every 4–6 weeks to determine the need for ongoing replacement therapy.[2,8] The patient should also be counselled regarding the need for high-dose steroid supplementation during intercurrent illness (i.e. surgery, infections, trauma, and major stressors) for up to 1 year after steroid discontinuation, as suppression of the hypothalamic–pituitary–adrenal axis can persist for months once steroids are withdrawn.[2]

In the case of our patient, the dose was tapered with a good clinical response. However, in order to avoid iatrogenic Cushing's syndrome and potential adrenal insufficiency, combining cytochrome P450 34 A inhibitors with ICS should be avoided, particularly PI and fluticasone, as mentioned above.

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